Brain activity modifications following spinal cord stimulation for chronic neuropathic pain: A systematic review

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Database: MEDLINE, PubMed, and EMBASE databases have been searched from 1967 (when SCS was first described) to 31 December 2014.

What does this review add?

- To our knowledge, this is the first systematic review regarding the effects of Spinal Cord Stimulation on brain activity.
- This review draws together the existing knowledge from functional imaging literature on the effects of SCS on the brain.
- This review highlights gaps in current knowledge and stresses the importance of continued research in this field, suggesting directions for future research which could significantly enhance understanding of the supraspinal mechanisms of Spinal Cord Stimulation.

Abstract:

Background and objective: Spinal Cord Stimulation is believed to exert supraspinal effects; however these mechanisms are still far from fully elucidated. This systematic review aims to assess existing neurophysiological and functional neuroimaging literature to reveal current knowledge regarding the effects of SCS for chronic neuropathic pain on brain activity, to identify gaps in knowledge, and to suggest directions for future research.

Databases and data treatment: Electronic databases and hand-search of reference lists were employed to identify publications investigating brain activity associated with SCS in patients with chronic neuropathic pain, using neurophysiological and functional neuroimaging techniques (fMRI, PET, MEG, EEG). Studies investigating patients with SCS for chronic neuropathic pain and studying brain activity related to SCS were included. Demographic data (age, gender), study factors (imaging modality, patient diagnoses, pain area, duration of SCS at recording, stimulus used) and brain areas activated were extracted from the included studies.

Results: Twenty-four studies were included. Thirteen studies used neuroelectrical imaging techniques, eight studies used haemodynamic imaging techniques, two studies employed both neuroelectrical and haemodynamic techniques separately, and one study investigated cerebral neurobiology.

Conclusions: The limited available evidence regarding supraspinal mechanisms of SCS does not allow us to develop any conclusive theories. However, the studies included appear to show an inhibitory effect of SCS on somatosensory evoked potentials, as well as identifying the thalamus and anterior cingulate cortex as potential mediators of the pain experience. The lack of substantial evidence in this area highlights the need for large scale controlled studies of this kind.

Introduction

Spinal cord stimulation (SCS), since its initial report in 1967 (Shealy et al., 1967), has provided substantial pain relief for many patients suffering from chronic neuropathic pain. The treatment initially emerged following the development of the Gate Control Theory (Melzack and Wall, 1965) which suggested that the transmission of pain signals could be inhibited at the dorsal horn of the spinal cord by the stimulation of large-diameter nerve fibres. The effectiveness of SCS for the management of complex regional pain syndrome (Kemler et al., 2000) and failed back surgery syndrome (Kumar et al., 2007) has been confirmed by randomised controlled trials. The analgesic mechanisms of SCS at a spinal level have been well documented (Linderoth and Foreman, 1999; Linderoth, 2009; Meyerson and Linderoth, 2006) and the existence of descending inhibitory processes stemming from a cortical level during chronic pain is widely accepted (Tracey and Mantyh, 2007; Tracey, 2008). However, the effect that SCS has on these supraspinal processes is still far from fully elucidated. Neurophysiological and functional neuroimaging techniques provide a unique means of non-invasively studying these processes and increasing our understanding of the underlying mechanisms of SCS.

To our knowledge, the functional imaging literature regarding the effects of SCS on human brain mechanisms has not been systematically reviewed. This systematic review assesses the published work investigating the effects of SCS for chronic neuropathic pain on cortical and subcortical processing, as elucidated by neurophysiological and functional imaging techniques. The aim of this systematic review is to reveal the extent of current knowledge, identify knowledge gaps and suggest directions for future research.

Methods

Search strategy

Publications which addressed the effects of SCS on human brain activity in chronic pain patients were reviewed. We searched MEDLINE, PubMed, and EMBASE electronic databases from 1967 (when SCS was first described) to 31 December 2014. A combination of MeSH and free-text terms were used, including: spinal cord stimulation; SCS; neurostimulation; functional magnetic resonance imaging; fMRI; positron emission tomography; PET; electroencephalography; EEG; magnetoencephalography; MEG; and somatosensory evoked potentials. The search was restricted to English language publications involving human participants. Hand-search of the reference lists of all included articles were also explored for further relevant papers.

Selection of studies

Papers were included in the review if they met the following inclusion criteria: (i) patients were treated using SCS for chronic neuropathic pain; (ii) a technique was employed to investigate brain activity related to SCS. Publications were excluded from the review if they met any of the following exclusion criteria: (i) articles were reviews, not presenting original research or abstracts of conference proceedings for which no full peer-reviewed articles have been published; (ii) they did not include SCS patients; (iii) patients were being treated with SCS for conditions other than chronic neuropathic pain (e.g. angina pectoris) or type of pain was not specified; (iv) techniques employed were not measuring brain activity. An initial screen of titles and abstracts retrieved by the search was conducted by two independent reviewers (LDB and RVD). Full texts of all potentially eligible studies were retrieved. Two review authors (LDB and RVD) independently examined these for compliance with the inclusion criteria and selected the appropriate studies. Disagreements as to eligibility were resolved by discussion or by a third review author (JHR).

Data extraction

Data from eligible studies was extracted using a data extraction form designed for this review. Data extracted included study characteristics and outcome data. Data collected with the data extraction form included: author, date of publication, patient factors (age, gender), study factors (imaging modality, patient diagnosis, pain area, duration of SCS at recording, stimulus used) and brain areas activated. Where studies had multiple publications (e.g. conference abstract and full paper), we used the main report as the reference and derived additional details from secondary papers. Data extracted is reported descriptively.

Results

From 1277 articles which were identified as potentially eligible for inclusion in this review, 33 met our inclusion criteria (Fig. 1). After scrutiny of the full-text publications, a further nine publications were excluded: four were abstracts of conference proceedings, two of which had no full-text publication available for further clarification of study factors (Buonocore and Demartini, 2014; Oluigbo et al., 2012), and two of which presented data which was also available in full-text articles included within this review (Moens et al., 2012b, 2013b); two reviewed previous research and were not presenting original data (García-Larrea et al., 2000; Zonenshayn et al., 2000); one did not specify the type of pain being investigated (Balzer et al., 2011); one was not measuring brain activity (North et al., 2012); and one was not investigating the effect of SCS on brain activity (Paradiso et al., 1995).

Twenty-four studies were included in the systematic review: thirteen used neuroelectrical imaging techniques (de Andrade et al., 2010; Augustinsson et al., 1979; Blair et al., 1975;

Buonocore et al., 2012; Doerr et al., 1978; Gildenberg and Murthy, 1980; Pahapill and Zhang, 2014; Pluijms et al., 2015; Poláček et al., 2007; Schlaier et al., 2007; Schulman et al., 2005; Theuvenet et al., 1999; Wolter et al., 2013); eight used haemodynamic imaging techniques (Hosobuchi, 1985; Kiriakopoulos et al., 1997; Kishima et al., 2010; Kunitake et al., 2005; Meglio et al., 1991; Moens et al., 2012a; Nagamachi et al., 2006; Stančák et al., 2008); two used both neuroelectrical and haemodynamic techniques, which are discussed respectively in the following two sections (Mazzone et al., 1995; Sufianov et al., 2014); and one investigated cerebral neurobiology, which is discussed within the section on haemodynamic studies (Moens et al., 2013a). The results of the study selection process are displayed in Figure 1.

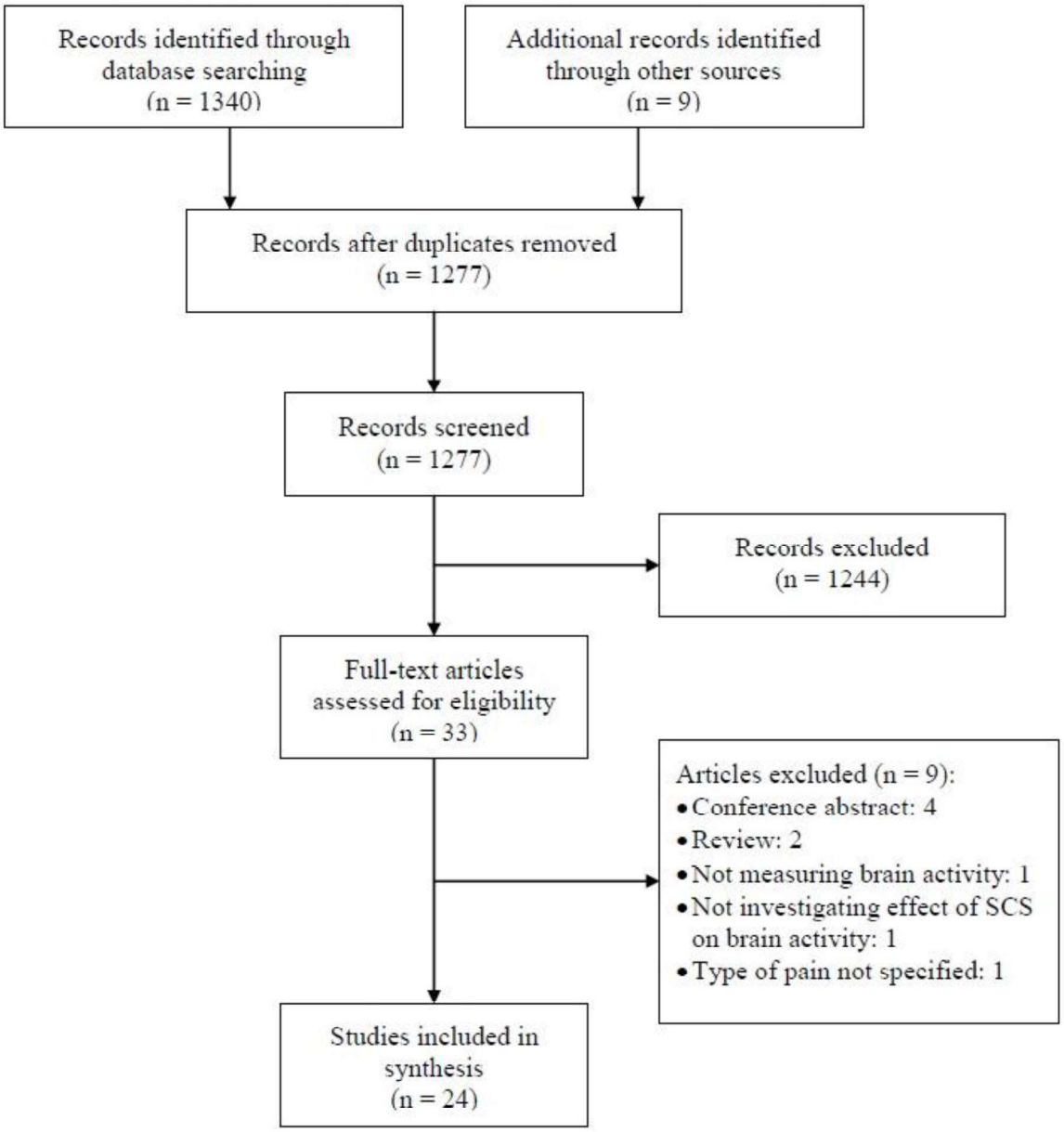

Figure 1: Results of study selection process

Neuroelectrical studies

Fifteen papers included in this review involved the implementation of neuroelectrical imaging techniques (electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), intracranial recordings) to study the effect of SCS on cortical processing (Table 1). These studies largely examined this effect by investigating the influence of SCS on somatosensory evoked potentials/magnetic fields (SEPs/SEFs) to either innocuous or painful peripheral nerve stimulation. In particular, seven of the neuroelectrical studies in this review used EEG to investigate the effects of SCS on SEPs following innocuous tibial nerve stimulation (de Andrade et al., 2010; Blair et al., 1975; Buonocore et al., 2012; Mazzone et al., 1995; Poláček et al., 2007; Theuvenet et al., 1999; Wolter et al., 2013). Of these studies, all except one found SCS to have an inhibitory effect on the amplitude of these responses, however the latency of this attenuation differed across the studies. The study which did not find a clear inhibitory effect only observed an SCS related change in the later P300 component, with this component appearing in one patient, increasing in amplitude in one patient and remaining unchanged in a further two (Mazzone et al., 1995). Although not unanimous, the results of these studies along with others using MEG or different types of peripheral nerve stimulation strongly suggest that SCS may contribute to an inhibitory effect on somatosensory processing in the cortex. In addition to this, intracerebral recordings also found evidence suggesting that SCS modifies evoked responses to innocuous and painful peripheral nerve stimulation at a thalamic level (Augustinsson et al., 1979; Gildenberg and Murthy, 1980).

It was also observed that SCS was able to reverse cortical disorganisation of digit representations in the primary somatosensory cortex (S1) (Pahapill and Zhang, 2014) and that patients treated successfully with SCS show a comparable cortical power spectra to that of healthy controls (Schulman et al., 2005). Furthermore, the only TMS study conducted within this research area found that SCS normalised intracortical facilitation, suggesting that SCS may also have an effect on cortical excitability and neurobiological processes at a supraspinal level (Schlaier et al., 2007). These studies demonstrate the possible role of SCS in transforming pathological cortical processing in patients with chronic pain into a more healthy state of cortical functioning.

Table 1: Summary of findings from neuroelectrical studies investigating the effect of SCS on cortical processing

	Imaging modality	N[a]; Gender	Age[b]	Patient diagnoses	Pain area	Duration of SCS at recording	Stimulus	Findings
de Andrade et al. 2010	EEG	20; 12 Male	49.1 (36-66)	FBSS	Legs & low back	1-13 years (Mean = 5.7 years)	Tibial nerve stimulation (motor twitch)	SCS ↓ P40-SEP amplitude
Poláček et al. 2007	EEG	9; 4 Male	Range 37-58	FBSS	Left leg/lower back	12-43 months	Tibial nerve (motor threshold) & sural nerve (10% > pain threshold) stimulation	SCS ↓ SEP amplitude in cS1, bS2, & MCC to tibial nerve stimulation. SCS ↓ PREP amplitude in cS1 & bS2 but ↑ PREP amplitude in MCC to sural nerve stimulation
Sufianov et al., 2014	EEG	30; 18 Male	48.7 ± 2.3	FBSS	NR	Pre-implant & 3 months post-implantation	Resting state recordings pre- and post-implantation of SCS	*Pre-SCS:* ↓ α -band frequency & ↑ δ -, θ -, & β -band amplitudes compared to healthy controls *Post-SCS:* normalisation of α -band frequency & normalisation/significant amplitude ↓ across the total frequency range
Buonocore et al. 2012	EEG	10; 4 Male	55.3 (42-72)	FBSS, lumbar radiculopathy, polyneuropathy	Legs	NR	Tibial nerve stimulation (motor twitch)	SCS ↓ amplitude of P39N50 component. Amplitudes returned to baseline with SCS off again
Wolter et al. 2013	EEG	10; 4 Male	54 ± 10.2 (40.7-77.2)	FBSS, neuropathic knee pain	Legs	3.9 ± 3.8 years (0.2-12.3)	Tibial nerve stimulation (motor twitch)	SCS & TENS ↓ amplitude of P40N50 (S1) SEP component but SCS showed greater attenuation. SCS ↓ amplitude of N50P60 SEP component
Pluijms et al. 2015	EEG	15; 8 Male	59.9 (50-72)	Diabetic polyneuropathy	Legs	Pre-implant & 2 weeks post-implant (trial SCS)	CHEPs at dorsal forearm, volar forearm, & lower leg	*Pre- vs Post-SCS:* Dorsal P2 latency ↓ post-SCS. *SCS Responders vs Non-responders:* Volar forearm N2 & dorsal forearm N2 & P2 latencies ↑ in SCS responders.
Blair et al. 1975	EEG	6; 3 Male	Range 28-52	Lumbar radiculopathy, cauda equina syndrome, chronic pancreatitis	NR	≤ 1 month	Tibial nerve stimulation (motor twitch)	SCS ↓ amplitude of late SEP components (200-300ms). Greater than clinically relevant SCS intensities ↓ amplitude of all SEP components

Mazzone et al. 1995	EEG	4; 2 Male	Range 22-78	Mixed pathologies	NR	NR	Tibial nerve stimulation (20% above sensory threshold)	No change to early SEP components with SCS. P300 component appeared in 1 patient, ↑ in amplitude in 1 patient and remained unchanged in 2 patients with SCS
Doerr et al. 1978	EEG	25; 25 Male	Range 35-60	Post amputation pain, brachial plexus lesion	NR	NR	Median nerve stimulation (motor threshold)	No change to SEPs with SCS
Theuvenet et al. 1999	EEG/MEG	3; 2 Male	Range 47-69	Mixed neuropathies	Foot/hand	3 days pre-implant; trial SCS; 6 months-3 years post-implantation	Median & posterior tibial nerve stimulation (motor twitch)	SCS ↓ amplitude of 80-150ms SEP/SEF component
Pahapill & Zhang 2014	MEG	1; Female	41	CRPS type 1	Right arm	NR	Tactile finger stimulation	Disorganisation/inversion of D1/D5 cortical representation in S1 was normalised with SCS
Schulman et al. 2005	MEG	5; Gender NR	41.5 ± 6.95 (35-51)	FBSS, mixed neuropathies	Legs/back	NR	Spontaneous eyes-closed recording during post-SCS analgesia	Power spectra of patients with >50% pain relief with SCS was comparable to healthy controls
Augustinsson et al. 1979	Intracerebral recording	1; Male	35	Stump & phantom limb pain	Right stump & phantom leg	2 years	Peroneal nerve stimulation to increase stump pain	SCS ↑ amplitude of early PREP components & ↓ amplitude of late PREP components in cVL
Gildenberg & Murthy 1980	Intracerebral recording	2; Gender NR	NR	Stump & phantom limb pain, arachnoiditis	Right stump & phantom leg; upper and lower limb pain	NR	Painful and non-painful median, sciatic, or sural nerve stimulation	Short-latency SEP in VPL not affected by SCS. SCS modified 80-150ms SEP component in IL
Schlaier et al. 2007	TMS	5; 4 Male	Range 39-50	Radiculopathy	Legs/Low back	NR	Motor cortex stimulation	ICF ↑ with SCS off and then reverted to baseline with SCS on again

Abbreviations: α, alpha; β, beta; δ, delta; θ, theta; b, bilateral; c, contralateral; CHEPs, contact heat evoked potentials; D1, first digit; D5, fifth digit; EEG, electroencephalography; FBSS, failed back surgery syndrome; ICF, intracortical facilitation; IL, intralaminar nucleus; MCC, midcingulate cortex; MEG, magnetoencephalography; NR, not reported; PREP, pain-related evoked potential; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SCS, spinal cord stimulation; SEF, somatosensory evoked magnetic field; SEP, somatosensory evoked potential; TMS, transcranial magnetic stimulation; VL, ventrolateral thalamus; VPL, ventral posterolateral nucleus

[a] = number of SCS patients

[b] = mean age (unless otherwise stated)

Haemodynamic studies

Ten papers investigated the effects of SCS on cortical processing using haemodynamic imaging techniques (functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), 133-Xe inhalation). These studies found a range of activity across several regions of the pain matrix, as identified by increases and decreases in regional cerebral blood flow (rCBF) (Table 2). Activity across these regions varied greatly between studies; however there appears to be a trend towards increased activity in frontal regions of the cortex, as well as identifying the anterior cingulate cortex (ACC) and thalamus as mediators of the pain experience and potentially key components of the influence of SCS at supraspinal levels.

Additional findings (which were not displayed in Table 2 in order to ease comparison between studies) include differences in the velocity of regional cerebral blood flow (rCBF) changes dependent on the spinal cord level being stimulated and differences between good and poor responders to SCS. An increase in velocity of rCBF was most commonly found when stimulating at cervical levels of the spinal cord (Meglio et al., 1991). When looking at potential differences in brain activity between good and poor responders to SCS, the main difference found between the two groups was observed at baseline. Prior to stimulation, poor responders to SCS showed increased thalamic activation, whereas good responders showed almost no activation in the thalamus (Nagamachi et al., 2006).

Cerebral neurobiological changes in response to SCS were also investigated in one study, which has not been included in the Table 2 as the study factors differ significantly from the other identified papers. Using Proton Magnetic Resonance Spectroscopy (1H-MRS), increases in γ-aminobutyric acid (GABA) and decreases in glucose in the ipsilateral thalamus were observed as a result of SCS (Moens et al., 2013a). This study further highlights the possible key role of the thalamus in the pain relieving mechanisms of SCS treatment.

Table 2: Summary of findings from haemodynamic studies investigating the effect of SCS on cortical processing

	Imaging modality	N[a]; Gender	Age[b]	Patient diagnoses	Pain area	Duration of SCS at recording	Areas showing increased rCBF with SCS	Areas showing decreased rCBF with SCS
Moens et al. 2012a	fMRI	20; 7 Male	Range 35-80	FBSS	Back/legs	Trial SCS	NA	b. Med. Thal, bACC, bPCC, i. Dors. PMC, i. Ant. Insula, i. LN, i. CN, iS1, iS2, cHPT, c. Insula, cS2, c. proprioceptive cortex, cVC, cPHG
Stančák et al. 2008	fMRI	8; 5 Male	Range 34-58	FBSS	Low back/legs	Trial SCS	*SCS only:* M1, iS2, c. Post. Insula *SCS & Acute heat pain:* Lt. ITG, Rt. MTG, i. cerebellum	*SCS only:* bM1, Lt. PSTS, Lt. temporal pole
Kiriakopoulos et al. 1997	fMRI	3; 3 Female	Range 34-48	FBSS, CRPS, cauda equine syndrome	Low back/buttock/legs	Trial SCS	S1, S2, bACC	NA
Kishima et al. 2010	PET	9; 6 Male	Range 28-65	FBSS, CRPS, cerebral haemorrhage, spinal injury	Legs	6-12 months	Rt. Thal, Rt. OFC, Lt. Inf. PC, Rt. Sup. PC, Lt. ACC, Lt. DLPFC	NA
Sufianov et al., 2014	PET	30; 18 Male	48.7 ± 2.3	FBSS	NR	Pre-implant & 3 months post-implantation	*Pre-SCS:* PCG, OFC, Thal, ACG *Post-SCS:* OFC & ACG markedly ↓ but still significantly greater than healthy controls	*Post-SCS:* PCG & Thal activity normalised when compared with healthy controls
Kunitake et al. 2005	SPECT	11; 9 Male	61 ± 13 (30-76)	Mixed neuropathies	Neck/legs/arms	Trial SCS (6 patients); > 1 year (5 patients)	cThal (in central pain patients), bFC, bACC, cTC	cPC
Nagamachi et al. 2006	SPECT	18; 13 Male	47.5 ± 13.1 (33-63)	Mixed neuropathies	NR	Trial SCS	*Baseline:* b. Precuneus, b. Cerebellum *After SCS:* Activation disappeared or was markedly localised	*Baseline:* bSTG, bACG, b. Subcallosal gyrus *After SCS:* Greater decrease in bACG, normalised activity in b. Subcallosal gyrus, no change in bSTG

Hosobuchi 1985	133-Xe inhalation	10; 4 Male	43.6	NR	Leg/arm	3-4 weeks	Cervical SCS: i. hemisphere (medial/posterior regions)	NA
Mazzone et al. 1995	133-Xe inhalation	6; 3 Male	Range 16-78	Mixed pathologies	NR	NR	Global increase with acute SCS in 4/6 patients	NA
Meglio et al. 1991	133-Xe inhalation	8; Gender NR	NR	Mixed neuropathies	Arms/legs/chest	NR	Focal increase in 4/8 patients. Global increase in 2/8 patients.	Global decrease in 2/8 patients

Abbreviations: ACC, anterior cingulate cortex; ACG, anterior cingulate gyrus; Ant, anterior; b, bilateral; c, contralateral; CN, caudate nucleus; CRPS, complex regional pain syndrome; DLPFC, dorsolateral prefrontal cortex; Dors, dorsal; FBSS, failed back surgery syndrome; FC, frontal cortex; fMRI, functional magnetic resonance imaging; HPT, hypothalamus; i, ipsilateral; Inf, inferior; ITG, inferior temporal gyrus; LN, lentiform nucleus; Lt, left; M1, primary motor cortex; MT, medial thalamus; MTG, medial temporal gyrus; NA, not applicable; NR, not reported; OFC, orbitofrontal cortex; PC, parietal cortex; PCC, posterior cingulate cortex; PCG, postcentral gyrus; PET, positron emission tomography; PHG, parahippocampal gyrus; Post, posterior; PSTS, postcentral gyrus; rCBF, regional cerebral blood flow; Rt, right; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SCS, spinal cord stimulation; SPECT, single photon emission computed tomography; STG, superior temporal gyrus; Sup, superior, TC, temporal cortex; Thal, thalamus; VC, visual cortex

[a] = number of SCS patients

[b] = mean age (unless otherwise stated)

Discussion

Theories of SCS mechanisms

The results of this review do not allow the development of conclusive theories regarding the effect of SCS on cortical processing. However, some of the papers included do discuss potential mechanisms to explain the observed effects; particularly focusing on the collision of impulses theory and sensory 'gating' to explain the inhibition of SEPs/SEFs (Buonocore et al., 2012; Wolter et al., 2013). The collision of impulses theory proposes that two action potentials which are travelling in opposite directions (as would occur during SCS) should cancel each other out at the point of their collision; however this does not account for the increased activity found in many regions of the cortex, as highlighted by the haemodynamic studies in this review. Alternatively, the sensory gating hypothesis claims that the heightened somatosensory activity in the cortex as a result of SCS may diminish the cortical capacity to process pain; yet this theory does not account for why specific components of the cortical response to sensation and pain are inhibited while others may be intensified (Poláček et al., 2007). It has also been posited that the activation of thalamic and parietal regions during SCS may reflect the influence of this treatment over pain cognition; whereas activation of prefrontal regions and the ACC which is displayed across many of the haemodynamic studies in this review may reflect the influence of SCS over the emotional aspects of pain (Kishima et al., 2010). Despite these theories explaining aspects of the findings regarding the influence of SCS on cortical processing, it is apparent that they remain unable to fully explain the experience.

Limitations of studies

A crucial finding from the present review is that the vast majority of papers currently available in this research area possess important limitations. Around half of the papers included within this review are over fifteen years old, using far more rudimentary imaging and analysis techniques than are currently available. Several of the studies included had very limited sample sizes, often investigating patients with heterogeneous pain areas and diagnoses. These patient samples also regularly included trial SCS patients for whom the efficacy of the treatment cannot be confirmed or failed to report the duration in which patients had been receiving SCS treatment.

Fundamentally, the reporting of results was poor across several of the studies including, in some cases, omission of basic information such as patient demographics. The presence of these limitations in so many of the available studies creates the potential for bias within these publications and subsequently for the outcomes of this review to have been skewed as a result.

A further fundamental limitation within this research area currently is that the experimental paradigms being employed often make it difficult to ascertain whether brain activity

modifications are occurring as a result of spinal cord stimulation itself or whether they are due to the pain relief achieved with this treatment. Therefore, it is important to maintain a relative amount of caution when interpreting the results of studies in this research area, and in turn those of this review.

Due to these limiting factors and the large variation between studies both in terms of patient samples and methodology, the data collected as part of this review was only able to be reported descriptively, making it extremely difficult to draw meaningful conclusions regarding the mechanisms of SCS in the cortex. However, these limitations only seek to further highlight the importance of continued high quality research in this area.

Directions for future research

In order for future research to draw us closer to developing robust theories regarding the effect of SCS on supraspinal processing, it is fundamentally important that research in this area continues in a methodologically controlled and consistent manner, utilising advancements which are made both in neuromodulation and functional neuroimaging to construct more sophisticated paradigms. SCS technology has developed to produce devices which are MRI compatible, and these are now far more frequently implanted. Involving these patients in research will not only allow for more refined haemodynamic studies using techniques such as fMRI, but also for more accurate coregistration and analysis of data acquired using methods such as EEG and MEG.

In addition to technological advancements in the MRI-compatibility of SCS devices, novel stimulation techniques have also been developed more recently, such as high-frequency SCS (Van Buyten et al., 2012). This stimulation technique provides analgesia for patients suffering from chronic neuropathic pain conditions, without producing the paresthesia associated with conventional SCS. Researching the brain activity modifications of conventional SCS does not easily lend itself to study as part of a blinded, randomised controlled trial which would hold more predictive power, due to the paresthesia that patients feel during the treatment. Although the long-term success of high-frequency SCS is yet to be determined, the study of patients with this type of SCS treatment could provide a means of investigating the associated supraspinal mechanisms as part of a blinded, controlled trial; thus overcoming the potential confounds associated with placebo effects and patient expectations.

Future research could also further utilise paired-pulse TMS to investigate the effect of SCS on cortical excitability. Normalisation of this excitability, as shown by decreases in intracortical facilitation following SCS was described for the first time by one paper within this review (Schlaier et al., 2007). This study highlighted the possible role of SCS in modulating neurobiological processes at a supraspinal level. Thus, in terms of increasing

understanding of the complex interplay of mechanisms likely to be involved in the analgesic effects of SCS treatment, this is an area which undoubtedly warrants further exploration.

Much of the research currently available in this field is diminished by the use of extremely small, heterogeneous patient samples. Both fMRI and MEG studies require a sample size that should be based on the variability of the measured parameter (standard error of the judgement criteria). Defining a priori the parameter of interest, the variability of this parameter and the difference being measured (between two groups or conditions) will provide an estimate of minimum sample size. It has been suggested that for studies using fMRI, a minimum sample size of 12 participants should be used in order to obtain 80% power with an error threshold of 5% at a single voxel level (Desmond and Glover, 2002). However, when correcting for multiple comparisons, many more patients are needed; thus much larger sample sizes are often required to draw firm conclusions. Several factors can be optimised in order to minimise required sample sizes; reducing within-subject variation when using repeated measures study designs, maximising the effect of the intervention to enhance the difference between control and experimental conditions, and conducting 'region of interest' rather than whole-brain voxel-wise analyses helps to overcome the problem of multiple comparisons and therefore reduce sample size requirements (Zandbelt et al., 2008). To our knowledge, similar papers have not been published to give clear guidelines for minimum sample sizes using the other neurophysiological and functional imaging techniques employed in the studies highlighted within this review. Guidelines which provide recommendations for good practice in the acquisition, analysis, and reporting of MEG studies are currently available, but these make no estimations of minimum sample sizes for MEG studies (Gross et al., 2013). As suggested in the MEG good practice recommendations, it is possible to increase the validity of the tests if the scope of the statistical analysis is limited a priori (Gross et al., 2013). The number of these tests should be limited to the essential minimum and multiple tests only performed for data dimensions for which the researcher has no prior hypothesis (Gross et al., 2013). If we accept that a minimum sample size of 12 participants is needed in fMRI studies to obtain sufficient power, this indicates that 2/3 of the fMRI studies in this review are underpowered. Similarly, if we accept that minimum sample sizes for other neurophysiological and functional imaging studies should be around the same level as those estimated for fMRI, this highlights that the majority of studies within this review are underpowered due to limited samples. Within this research area, researchers should strive to study larger groups of patients with homogenous underlying pain conditions and symptom presentations, as well as ensuring patients which are being classed as good responders to the treatment have had fully implanted SCS therapy for a sufficient length of time to ensure that they are not simply having a placebo response to receiving treatment.

This field of research needs to take into consideration potential confounding factors when interpreting results. This is the matter of identifying whether modifications in brain activity which we observe are actually directly related to the mechanisms of SCS or whether they are

occurring as a result of the pain relief attained with this treatment. Many SCS patients report that the pain relief they gain from this treatment does not occur instantaneously when stimulation is switched on. Therefore, one way in which research could address this confound would be by studying patients for which pain relief from SCS treatment is not immediate and investigating possible differences in cortical activation when patients are receiving SCS, between periods of time when their pain levels are still reflective of their clinical pain experience without stimulation and time periods when they have reached the peak of the analgesia they achieve with SCS. Identifying potential differences between these conditions would be particularly suited to study using techniques such as MEG and EEG which are well suited to identifying temporal changes in cortical activity.

Knowledge in this area may also be significantly enhanced if future research were to focus on investigating any differences in cortical processing between patients for whom SCS successfully manages their chronic pain conditions and those with homogeneous diagnoses and symptom presentations that have little or no success with SCS treatment. Differences between these two groups were the focus of two papers included in this review, which observed increased contact heat evoked potentials (CHEPs) latencies in SCS responders when compared with non-responders (Pluijms et al., 2015), as well as identifying the thalamus as a possible contributor to the effectiveness of SCS (Nagamachi et al., 2006). With further detailed research undertaken, this research focus has the potential of identifying biomarkers which could determine treatment success and in turn, assist in the screening process of future SCS patients.

Conclusions

This is the first systematic review of the effects of SCS on cortical processing. The findings of this review suggest that SCS may play an inhibitory role in somatosensory processing, as well as recruiting regions of the pain matrix most closely associated with cognitive and emotional aspects of pain processing. However, this review also highlights the current lack of consensus and detailed understanding regarding the effect of SCS on the cortex; thereby emphasising the importance of further investigations in a more controlled manner. SCS remains a treatment which can produce life-changing pain relief for many patients with chronic neuropathic pain, and already significant progress has been made in the development of this neuromodulatory technique since its emergence. However, in order to continue to develop and understand this treatment, it is important that future research draws on these technological advancements to construct more controlled and sophisticated experimental paradigms, as well as investigate the cortical processes that differentiate between treatment success and failure.

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